REMARKS

Status of the claims

Claims 2, 4, 8, 16, 17, 36 – 39, 41, 42, and 46-49 are currently pending in the application

Method claims 26 – 35 and 40 remain withdrawn to be considered for rejoinder at such time as allowable composition claims are identified.

Applicants believe that claim 41 which depends from an allowable claim should be rejoined and accordingly have indicated that claim as pending.

Applicants thank the Examiner for the indication that claims 4, 16, 17, 36-39 and 41 are allowed.

1. Objections withdrawal and claim rejoinder

The Office Action indicates that claims 4, 16, 17, 36, 37, 41 were previously objected to in the Office Action of August 24, 2005 as depending on rejected claim 2. After the amendment previously filed by Applicants the claims are no longer dependent on rejected claim 2 and thus the objection is withdrawn.

The Office Action indicates that claim 4 is directed to an allowable product and that pursuant to the procedures set for in MPEP, claims 38-39 and 40 directed to the process of making or using the allowable product, previously withdrawn from consideration as a result of a restriction requirement are rejoined and examiner. However, at the top of page 2, the Office Action indicated that claim 40 would not be rejoined and examined. Applicants believe that the Examiner meant that claim 41 should be rejoined as it also depends from allowed claim 4. This agrees with the list of allowed claims on the first page of the office action. Applicants request that upon an indication that claim 2 is allowed that claim 40 be rejoined.

2. Rejections under 35 U.S.C. §112, second paragraph

Applicants thank the Examiner for an indication that the rejection of claim 42 is withdrawn. Rejection of claims 43-45 is moot because the claims have been canceled.

3. Rejections under 35 U.S.C. §112, first paragraph

Applicants thank the Examiner for an indication that the rejection of claim 42 is withdrawn. Rejection of claims 43-45 is moot because the claims have been canceled.

4. Rejections under 35 U.S.C. §103

Claims 2, 8, 42 and 49 stand rejected under 35 U.S.C. § 103 as being unpatentable over Urwin et al. (Planta, 1998, 204, 472-479) andWO 92/10575 (1992) in view of Bingle et al. (Thorax, Dec. 1996, vol. 51/12, pages 1273-1274).

Applicants respectfully traverse.

The present claims are directed to a fusion protein having a funcationally active portion of alpha 1-antitrypsin and a functionally active portion of secretory leukocyte protease inhibitor, wherein said fusion protein has alpha 1-antitrypsin protease inhibitor activity and secretory leukocyte protease inhibitor activity. Both of the activities are found in a single fusion protein and are derived from the functionally active portion of the respective individual protease inhibitors. In addition, claim 42 recites that the functionally active portion of alpha 1-antitrypsin comprises-an elastase inhibitory domain and the functionally active portion of secretory leukocyte protease inhibitor comprises an elastase inhibitory domain.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990)

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466

(Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 ("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.").

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the prior art references alone or in combination fail to teach or suggest the claimed invention.

Bingle has been described previously. This reference discloses potential combination therapy of SLPI and α-PI in the treatment of various disorders. As has been discussed before., it is agreed that Bingle neither teaches nor suggests fusing SLPI to AAT to create the singular molecular entity fusion proteins of Applicants' claims 2, 8 and 42. In addition, Applicants submit that Bingle fails to disclose a fusion of functionally active fragments of these molecules. Bingle fails to teach or suggest that fusion molecules of SLPI and AAT would be active upon fusion. The fusion of the molecules could result in an altered conformation which would prevent binding of the molecules to the elastase or activity. Finally, Bingle teaches away from combining the AAT to SLPI. Bingle teaches that the interaction between SLPI and NE is reversible facilitating transfer of NE to AAT. Inactive NE-AAT complexes are cleared via the lymphatic vessels and blood, while SLPI is recycled. One skilled in the art would not want to combine SLPI to the AAT to result in inactive SLPI-AAT-NE complexes.

The Unwin reference teaches a dual protease inhibitor consisting of a cysteine and serine protease inhibitor joined as translational fusions by one of two peptide linkers. The fusion inhibitor is expressed in plants and ingested by nematodes. This reference does not teach or suggest the AAT protease inhibitor or the SLPI protease inhibitor, let alone the creation of a fusion protein comprising a functionally active portion of the AAT and a functionally active portion of the SLPI protease inhibitor. This reference teaches a fusion protein expressed in plant cells comprising protease inhibitors effective in nematodes upon ingestion. It does not teach the fusion of mammalian proteins. It does not teach the administration of proteins to mammals.

WO92/10575 teaches bifunctional inhibitors of platelet activation and thrombin. WO92/10575 does not teach or suggest the functionally active portion of the AAT or the

functionally active portion of SLPI. WO92/10575 does not teach or suggest a fusion peptide comprising the functionally active portion of the AAT and the functionally active portion of SLPI. WO92/10575 does not teach that a fusion peptide comprising the functionally active portion of the AAT and the functionally active portion of SLPI has a reasonable likelihood of been active.

Accordingly, there is no teaching or suggestion in the WO reference, Urwin or Bingle either alone or in combination of how to generate an active fusion protein of the functionally active portion of alpha 1-antitrypsin fused with the functionally active portion of SLPI. While the WO reference and Urwin do disclose fusion proteins of certain molecules, there is no mention of fusing SLPI or alpha 1-antitrypsin or functionally active fragments of the two. Bingle does not teach fusing the functionally active fragments of the two molecules. None of the references teach how to link the functionally active portions of AAT to SLPI to result in a functionally active fusion peptide. As such, the cited references fail to disclose the claimed invention.

Secondly, the references alone, or in combination, do not provide any motivation for the generation of a fusion molecule of functionally active portion of alpha 1-antitrypsin fused with functionally active portion of SLPI. Neither Unwin or the WO reference mention AAT or SLPI. The Office Action relies on a statement in Bingle as suggesting the fusion molecule. This statement is tentative at best when it states " probably the most effective treatment would entail combining SLPI and α-PI, particularly since oxidised SLPI unlike oxidized α-PI, remains a potent protease inhibitor, especially at high concentrations and despite containing methionine at its NE inhibitory site." However, Bingle teaches away from a fusion molecule. One skilled in the art in considering Bingle would simply administer both compounds individually at the same time. One would not be motivated to go to the expense and difficulty to create a fusion protein when the benefits could be obtained by simply administering the compounds individually. Furthermore, Bingle teaches that SPLI first reversibly binds to NE. It then passes the NE to AAT for reversible binding and removal using the lymphatic system. One of skill in the art would not be motivated to generate a fusion molecule where the SPLI would be caught in an irreversible bond with AAT-NE and not available for mopping up remaining free NE.

Finally, none of the references, either alone or in combination teach that the fusion molecule of the functionally active portions of the AAT and SLPI molecules has a reasonable expectation of success. There is no teaching that the molecules will retain their activity once fused. Bingle teaches away by teaching that SLPI remains potent when oxidized, in contrast to AAT, which does not. Bingle also teaches away by teaching that the molecules bind to different regions of NE. There is no reasonable expectation that a fusion molecule would result in a conformation of the functional regions such that they would be able to bind and inhibit the elastase molecule. Accordingly, one skilled in the art would not have a reasonable expectation of success.

Accordingly, Applicants respectfully request the Examiner to withdraw this rejection.

CONCLUSION

Applicants submit that the present claims are in condition for allowance, and respectfully request that withdrawn method claims be rejoined and examined. If the Examiner believes that any matters remain outstanding, however, applicants respectfully invite the Examiner to call the undersigned to schedule a telephonic interview.

Respectfully submitted,

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